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Molecular Insights into the Role of Inflammation and Oxidative Stress in Epilepsy

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Authors' contributions

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

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ABSTRACT

Epilepsy is a chronic neurological disorder manifested as unpredictable, unprovoked recurrent seizures that affect a variety of mental and physical functions. Despite the use of current anti-epileptic drugs (AEDs) about 30% of patients remain refractory, while 30-40% have associated psychiatric disturbances. A gap in successful AED search has been the lack of understanding of the processes leading to the cascade of epilepsy. Thus we tried to focus on the role of inflammation and oxidative stress in epilepsy. Epileptic seizures result in extensive release of proinflammatory factors i.e cytokines, chemokines from glial cells, thereby increasing the influx of neuronal calcium, enhancing extra neuronal glutamate concentration and decreasing potassium, resulting in decrease

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in seizure threshold and neurodegeneration. Prolonged seizures produce sufficient cellular reactive oxygen species (ROS) and reactive nitrogen species (RNS) which initiate a cascade of events induced by increased firing from neurons, excessive release of glutamate, activation of N-methyl-D-aspartate (NMDA) receptor, influx of cytosolic and mitochondrial calcium, increased ATP consumption and mitochondrial damage, resulting in neuronal hyperexcitation and neurodegeneration.

Keywords: Inflammation; oxidative stress; toll like receptors; blood brain barrier; epilepsy.

1. INTRODUCTION

Epilepsy is a chronic neurological disorder characterized by recurrent seizures and is often accompanied by psychiatric disturbances [1]. The excessive or synchronous neural activity in the brain leads to epileptic seizures [2]. Epilepsy represents a socioeconomic burden and usually patients suffering from epilepsy also suffer from social stigma. It affects almost 70 million people of world [3] including 10 million in India. The incidence of epilepsy for low-income and middle-income countries is estimated at 81.7/ 100,000/year, while for high-income countries it is estimated 45.0/100,000/year [4]. Similarly the prevalence of epilepsy for low and middle-income countries is about twice that of high-income countries [3]. The median life time epilepsy prevalence for low income and middle income countries is 15.4 per 1,000 for rural and 10.3 per 1,000 for urban areas while for high income countries it is 5.8 per 1,000. Similarly, the median active epilepsy for low-and middle-income countries is 12.7 per 1,000 in rural and 5.9 per 1,000 in urban areas and for high-income countries 4.9 per 1,000 [3]. Insult from seizures or excitotoxic brain damage induce, activate and persist regional as well as cellular patterns of inflammatory response to stimulate Toll like receptors (TLRs) which on activation stimulate various genes encoding proinflammatory factors such as cytokines, chemokines, complement system, cyclooxygenase-2 (COX-2), nitric oxide via many transcriptional factors or nuclear factors such as nuclear factor κB (NFκB) resulting in severe inflammation. The inflammatory responses induce oxidative and nitrosative stress pathways, while subsequent mitochondrial metabolic processes generate highly reactive free radical molecules. High levels of intracellular calcium ions also induce ROS production in a biosystem culminating in oxidative stress (OS) [5]. In this review we will discuss evidence for the role of inflammation and oxidative stress in epileptogenesis. A better understanding of these pathways may inform future treatment options.

2. INFLAMMATION IN EPILEPSY

Pathological conditions of brain inflammation are distinguished from normal physiological conditions because parenchymal cells (microglia, astrocytes, and neurons), blood brain barrier (BBB) and choroid plexus mediate production of detectable quantity of many inflammatory mediators which are usually produced in our body by the immune system either under pathological threats or in response to infection. A rapid and robust animal model for brain inflammation in rodents involves administering systemic infection mimicking lipopolysaccharide (LPS); the main structural component of external membrane of gram-negative bacteria and molecular patterns of invading pathogenic microbes, which are mainly recognized as sites for specific receptors: Toll like receptors (TLRs) and immune system cells.

These specific receptors (TLRs) get activated in presence of exogenous molecules and stimulate various genes encoding proinflammatory factors such as cytokines, chemokines, complement system, COX-2and nitric oxide via many transcriptional factors or nuclear factors such as nuclear factor κB (NFκB) [6]. Apart from infectious agents, inflammatory responses in brain are also well predicted against various endogenous ligands and signals usually sourced from a large spectrum of injuries i.e. trauma, ischemia during seizures, excitotoxic brain damage, damaged BBB or heat shock proteins of damaged extracellular matrix. Thus, if these ligands enter the brain, depending upon injury level they induce inflammatory response to stimulate TLRs, hence triggering many immune responses at various time functions [7].

2.1 Role of Blood Brain Barrier

Blood brain barrier (BBB) is made up of non fenestrated endothelial cells with tight junctions made up of interendothelial cells. The maintenance and functioning of BBB is regulated by various type of cells like pericytes,

perivascular microglia and astrocytes which are annexed to the capillary and post-capillary venules region in the central nervous system (CNS). BBB provides protection to CNS under normal physiologic conditions by strictly regulating the entry of plasma-born substances and immune cells into the nervous tissue. Transient changes in physiologic as well as structural characteristics of the BBB occur during events like seizures, traumatic and ischemic CNS injuries or pathogenic infections to the brain.

Brain regions characterized by a "leaky" BBB have been consistently reported in epileptic brain [8]. Seizures lead to the activation of IL-1β system and breakdown of the BBB [9]. This breakdown leads to the leakage of BBB and the entry of albumin into the brain. Albumin entry induces a further upregulation in inflammatory mediators and reduces potassium and glutamate uptake of astrocytes, culminating in elevated neural excitability [10]. Besides inflammatory reactions the invasions of leucocytes is also initiated due to BBB leakage [11]. Hence a breakdown of BBB has a net neuronal excitability effect.

In a seizure-related immune response, neurons are not the only brain cells to display an inflammatory phenotype in epileptic brain, since other brain cells also contribute to seizure related immune responses [12]. The chemokines and their receptors (CXCL12 and CXCR4; CCL2 and CCR2) are up-regulated in glia during seizures [13]. Adhesion molecules (P- and E-selectin) are also up-regulated in response to electrographic seizures at the luminal side of the endothelium forming the BBB [14].

Epileptic seizures also provoke such inflammatory responses which enhance calcium influx into neurons and activate glial cells. Glial cells increase extracellular potassium and glutamate and induce further inflammatory response which leads to a decrease in seizure threshold and neuronal hyperexcitability. Thus, epileptic seizures and inflammatory mediators form a positive feedback loop, reinforcing each other.

Thus two distinct inflammatory processes have been linked to seizures.

a) *Neuroinflammation* which is present in epileptic brain - where it exacerbates seizures or increases their frequency [15].

b) *Systemic inflammation* which causes epileptiform neuronal discharge via loss of ionic *e.g.* potassium and neurotransmitter *e.g.* glutamate homeostasis [16,10]. The neuroinflammation directly affects neurovascular and glial function. Systemic inflammation are mediated or facilitated by loss of BBB function [17].

2.2 Molecular Cascades

There are various pathways identified in hippocampus during the epileptic process. These include:

i. Disruption of BBB
ii. COX-2 signaling pathway and related prostaglandins
iii. Classical cytokines and their downstream targets
iv. TLRs.

During seizures, microglia and astrocytes are the first cells producing cytokines. These soluble proinflammatory cytokines function to communicate between microglia, astrocytes and the neurons [18]. The two inflammatory cytokines i.e. interleukin (IL)-1β and tumor necrosis factor (TNF)-α have their molecular as well as cellular actions on neuronal excitability and epilepsy. These molecules are released within the brain at specific circumstances. They modify both short-term and long-term neural excitability. The manipulation of IL-1β and/or TNF-α levels or their downstream pathways influences neuronal excitability, seizure susceptibility and epileptogenesis. IL-1β has a potential seizure facilitatory role in models of febrile seizures (FS), febrile status epilepticus (SE) [19] and pilocarpine-induced SE in immature rats [20]. Further enhanced endogenous IL-1β level reinforces its proconvulsant effects. Contrary to this, intracerebral application of natural antagonist of IL-1 receptor (IL-1ra) has been found to be powerful anticonvulsant agent, which simultaneously antagonizes the effect of endogenous IL-1β [21]. The mice exhibiting overexpression of IL-1ra shows significant reduction in susceptibility to seizures [22].

IL-1β binding to its receptor increases NMDA receptor-mediated Ca^{2+} influx and surface expression of AMPA receptors [23]. It inhibits glutamate reuptake by astrocytes [24] resulting in elevated extracellular glutamate levels and hyper-excitability. In hippocampal neurons reduction in magnitude of currents mediated by

γ-amino butyric acid (GABA) is counteracted by IL-1β [25].Thus one may envisage that functional interactions exist at the molecular level between IL-1β receptors and *N*-methyl-D-aspartate receptors (NMDA) which are co-expressed by hippocampal neurons [26]. The overexpression of IL-6 in glia cells increases seizure sensitivity towards glutaminergic agonists, although no such correlation is found with cholinergic agonists [27]. The overexpression of IL6 causes loss of GABA-and parvalbumin-positive neurons in the hippocampus of mice.

TNF-α is another inflammatory factor implicated in epilepsy, infact its expression is up-regulated in seizures [28]. Microglia in the brain mainly releases TNF-α [29] and stimulates astrocytes to release glutamate [30]. Glutaminergic neurons are stimulated because of extracellular increase in glutamate concentration thereby depolarizing their membrane potential. Thus post- seizure production of inflammatory mediators triggers neuronal hyperexcitability through modulations of ion channels via glutamate release in neurons and glia respectively. After ischemic, traumatic and excitotoxic damage in healthy brain tissue there is rapid induction in the level of proinflammatory cytokines such as TNF-α and interleukins which are initially expressing at very low level in normal brain [7]. Expression of messenger RNA (mRNA) and levels of proinflammatory cytokine proteins are enhanced with an exception for IL-1β which is upregulated in brain of rats developing spontaneous seizures even 60 days after the induction of status epilepticus. The status epilepticus or continuous seizures over 30 minutes can cause neuronal death [31] through glutamate-mediated excitotoxicity, necrosis and activation of apoptosis [32]. One to three days after status epilepticus, both neuronal and astrocytic death is observed in the dentate hilus region of hippocampus [33]. Injured neurons and glia and their fragmented DNA are rapidly cleared by activated microglia [34].

In addition to inflammatory cytokines, another major factor having a specific role in epilepsy are prostaglandins (PGs). Prostaglandins are major factors that stimulate inflammatory processes; they are markedly increased following seizures and contribute to epileptogenesis and reduction in seizure threshold [35]. With the robust production of PGs in the brain following seizures, an inducible type of COX, i.e COX-2 but not the constitutively expressed COX-1 is rapidly induced in the brain [36]. In hippocampal region, seizures induce COX-2 partly through the pathway of NMDA receptors [37,36,38]. When COX-2 is ablated from the principal forebrain neurons (e.g. hippocampal pyramidal and dentate granule neurons) there is no effect on seizure onset or intensity in the pilocarpine model, whereas selective ablation of COX-2 which is limited to principal forebrain neurons was neuroprotective in the hippocampus [39].

3. OXIDATIVE STRESS IN EPILEPSY

Oxidative stress (OS) and nitrosative stress (NS) are defined as imbalances between generation and elimination of reactive oxygen species (ROS) and reactive nitrogen species (RNS). Under normal physiological conditions ROS and/or RNS levels are fairly well regulated to perform important functions such as autophagy, chemical signaling, cell division, mitogen activated protein kinase signaling and apoptosis [40]. The ROS and RNS are highly reactive in nature, the imbalance of which is frequently associated with neurodegeneration and mitochondrial dysfunction seen with epileptogenesis [41]. In OS/NS there are alterations in ROS, RNS and nitric oxide (NO) signaling pathways, whereby bioavailable NO is decreased and ROS and RNS production is increased [42]. The inflammatory responses induce the OS and NS pathways, and subsequent mitochondrial metabolic processes generate highly reactive free radical molecules. ROS and RNS are generated during the irradiation of ultraviolet (UV), X-rays and gamma rays; they are produced by neutrophils and macrophages during inflammation; they include products of reactions catalyzed by metals present in air pollutants, and products of reactions catalyzed by the electron carriers in the mitochondria [43]. OS during SE induced by 4-aminopyridine, LiCl-pilocarpine or kainic acid has also been reported in immature rat brain, completely invalidating some views that SE-related OS is age-dependent [44].

Brain contains large number of easily oxidized fatty acids (20: 4 and 20: 6) and a limited antioxidant system and is thus highly sensitive to oxidative damage [45]. Oxidative stress is strongly implicated during seizures induced by excitotoxicity due to mitochondrial ROS generation [46,47]. During pilocarpine-induced SE, hyperactivity or excitotoxicity of neurons induce an increase in concentrations of free radicals [48]. The increased activity of glutaminergic systems induces status epilepticus

and there is a decrease in ATP levels due to change in redox potential, which leads to collapse in brain energy production and supply [49].

Seizures lead to an increase in glutamate release and activation of NMDA receptor with decrease in extracellular Ca^{2+} concentration and increase in cytosolic Ca^{2+} concentration [50]. The effects mediated by Ca^{2+} during excessive glutamate receptor activation (excitotoxicity) lead to neuronal degeneration and overload of mitochondria with Ca^{2+}, so free radicals are generated. Overload of this type of Ca^{2+} leads to OS, cellular damage, and eventually cell death because of Ca^{2+} mediated opening of mitochondrial permeability transition (MPT) pores associated with apoptosis [51].

The phospholipase A2-dependent activity of Ca^{2+} mediated by glutaminergic receptors liberates arachidonic acid (AA), which generates superoxide ($O2^{-}$) through its metabolism by lipoxygenases and cyclooxygenase for eicosanoid formation [52]. The constant formation of $NO^{\cdot}$ by the glia is neurotoxic because it increases the neuronal sensitivity to this reactive species. The neurotoxic action of $NO^{\cdot}$ is likely caused by the formation of Peroxynitrite ($ONOO^{-}$) which is rapidly formed by the reaction of $NO^{\cdot}$ with $O_2^{\cdot -}$. Xanthine oxidase generates $O_2^{\cdot -}$ when there is elevated intracellular Ca^{2+} concentration and energy deficiency.

3.1 Mitochondrial Dysfunction

Because of abundant mitochondria in neurons, demand of high aerobic metabolism as well as great load of iron the susceptibility towards oxidative damage is greatly enhanced in brain cells [53]. This extensive metabolic demand relates to the requirement of large amounts of ATP for neurotransmission as well as for maintaining ionic gradients across cell membranes in the neurons. Thus, neuronal performance critically depends upon mitochondrial function and oxygen supply as most of neuronal ATP production depends on oxidative metabolism [54]. Mitochondria have critical functions which influence neuronal excitability, excitotoxicity, ATP production, fatty acid oxidation, apoptosis and necrosis control, amino acid cycle regulation, biosynthesis of neurotransmitters and regulating the homeostasis of cytosolic calcium. Mitochondria are the main site of ROS production and are therefore extremely vulnerable to oxidative damage [55]. Prolonged seizures produce sufficient cellular superoxide ($O2^{-}$), principle by product of respiration, so initiate a cascade of events in the form of increased firing from neurons, excessive release of glutamate, activation of N-methyl-D-aspartate (NMDA) receptor, influx of cytosolic and mitochondrial calcium and increased ATP consumption. Thus, endogenous antioxidant defenses of mitochondria are overwhelmed resulting in mitochondrial damage [56, 57]. In SE, the levels of endogenous aconitase (marker of O_2) are decreased in rat hippocampus particularly in CA3 subregion [56]; moreover, SE impairs electron transport chain complexes (1, 3, and 4) [58] and there is reduction of mitochondrial N-acetyl aspartate (a metabolite synthesized from aspartate and acetyl-coenzyme A) in hippocampus [59]. Increase in mitochondrial H_2O_2 production, lipid peroxidation (increased malondialdehyde, MDA, and thiobarbituric acid, TBA) and mitochondrial DNA (mtDNA) damage are observed after a seizure [60]. An adaptive increase of mtDNA repair occurs immediately after ROS increase induced by acute SE. However, chronic increase in ROS production is accompanied by failure in the induction of mtDNA repair [61]. Damage to mtDNA and abnormal mitochondrial H_2O_2 production has been observed in the hippocampus of rats even three months after SE. After lithium-pilocarpine induced SE, OS markers (e.g. GSH) and specific markers of redox status in the mitochondria (coenzyme A) are decreased in the hippocampus and become permanently damaged during epileptogenesis and chronic epilepsy even when H_2O_2 production and mtDNA damage return to control levels [62]. Hence ROS formation contributes mechanically to chronic epilepsy via mitochondrial damage.

3.2 Impairment of Antioxidant Systems

During normal cellular metabolism various molecules are generated like ROS; including superoxide radical, hydrogen peroxide hydroxyl radical ($\cdot OH$) and singlet oxygen ($^1O2$). Physiological levels of ROS can be scavenged by enzymatic [e.g superoxide dismutase (SOD), glutathione peroxidase (GPx), catalase (CAT), glutathione reductase (GR), and peroxiredoxins (Prxs)] and non-enzymatic [e.g vitamin C, vitamin E and reduced form of glutathione (GSH)] antioxidant defense systems. However, excessive ROS levels due to increased ROS production, decreased antioxidant defense ability

or both leads to OS [63]. Superoxide radicals are highly reactive and can initiate pathological oxidative metabolism leading to the oxidation of macromolecules such as DNA, lipids and proteins. The nervous system contains antioxidant enzymes including SOD and GPx that are expressed in higher quantities than CAT [64]. This spectrum of enzymatic defenses suggests that the brain may efficiently metabolize superoxide, but may have difficulty in eliminating the hydrogen peroxide produced by this reaction (i.e., superoxide dismutation). Hydrogen peroxide accumulation is of major concern as the brain contains large quantities of iron and copper which may catalyze the formation of hydroxyl radicals that can induce lipid peroxidation [65]. Enhanced hydrogen peroxide in turn is reduced to water by peroxidases mostly GPx (and Prx) in the brain. GPx levels in neuronal tissue appear to be relatively low for the prevention of peroxide insults.

Neuronal cell membrane contains high levels of polyunsaturated fatty acids [66] and is more vulnerable to injury by lipid peroxidation products than other tissues [67]. Lipid peroxidation is an irreversible neuronal damage of cell membrane phospholipids and a possible mechanism of epileptic activity [48]. Vitamin E (α-tocopherol) is a lipophilic alcohol and its food source is the root of wheat and vegetable oils. This substance has the ability to prevent the negative effects of lipid peroxidation in the brain tissue because it can absorb free radicals of oxygen. Epilepsy patients on antiepileptic therapy coadministered Vit E exhibited further decrease in EEG recordings and seizure frequency [68].

4. CONCLUSION

The literature clearly indicates that Inflammation and OS are mediators of acute and chronic epilepsies. Disruption of the blood–brain barrier, the Cyclooxygenase signaling pathway and related prostaglandins, classical cytokines and their downstream targets, as well as Toll-like receptors are various pathways identified in hippocampus during epileptogenesis. These inflammatory responses promote neural hyperexcitability and neuronal degeneration. Seizures also dysregulate tightly regulated mechanisms for generation and elimination of ROS and RNS resulting in mitochondrial ROS generation, depletion of ATP stores and mitochondrial dysfunction, predisposing to neuronal hyperexcitation and neurodegeneration. The treatment strategies ameliorating proinflammatory and oxidative stress signals during seizure generation and epileptogenesis can seize the progression of disease.

CONSENT

It is not applicable.

ETHICAL APPROVAL

It is not applicable.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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